ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 12, pp.75903-75907, December, 2018
DOI: https://doi.org/10.24941/ijcr.33383.12.2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

SYNTHESIS AND BIOLOGICAL STUDY OF NOVEL TRIAZOLE ANALOGUES OF BENZOTHIAZEPINES

***Nagaraj, A., Srinivas, S. and Neelofer R.**

Department of Chemistry, Telangana University, Nizamabad, Telangana-503322 India

ARTICLE INFO

Article History:
Received 30th September, 2018
Received in revised form
09th October, 2018
Accepted 10th November, 2018
Published online 29th December, 2018

Key Words:
Triazole, Benzothiazepine,
Antibacterial activity.

ABSTRACT

A series of new 4-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-aryl-2,3-dihydro-1,5-benzothiazepine 6(a-j) have been synthesized from (*E*)-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-3-aryl-2-propen-1-one 5(a-j). The structures of the synthesized compounds have been confirmed via IR, ^{1}H NMR, ^{13}C NMR and MS spectral analyses. Further, all compounds have been assayed for their antibacterial activity against Gram-positive and Gram-negative bactiria. The antibacterial screening data revealed that, compounds 6 which contain 4-chlorophenyl (6b), 4-methoxyphenyl (6e) and 2-hydroxyphenyl (6f) moieties on benzothiazepine ring might be the reason for the significant inhibitory activity. Most of these new compounds showed appreciable activity against test bacteria and emerged as potential molecules for further development.

***Citation: Nagaraj, A., Srinivas, S. and Neelofer R.,* 2018.** "Synthesis and biological study of novel triazole analogues of benzothiazepines", *International Journal of Current Research*, 10, (12), 75903-75907.

INTRODUCTION

Benzothiazepine skeleton is an important moiety that has been widely used as building block for pharmaceutical agents (Bohrisch, 1994), and its derivatives are known to exhibit biological activities such as antifeedent (Reddy, 1993), coronary vasodilation (Glaser, 1989), tranquilizer (Oster, 1990), antidepressant (Vega, 1998), CNS stimulant (Vyawahare, 2010), antihypertensive (Inoue, 1991), calcium channel blocker (Inoue, 1971), antiulcer (Sachio, 1983), calmodulin antagonist (Suzuki, 1994), antioxidant (Feng, 2012) and antimicrobial (Wang, 2009) agents. Benzothiazepine derivatives have also been reported to be more potent selective inhibitors of the mitochondrial Na^{+}-Ca^{2+} exchangers (Chiesi, 1988). The broad spectrum of clinical importance and commercial success associated with benzothiazepines has led to their recognition in the medicinal chemistry (Renuka, 2014). Similarly, the triazole and its derivatives have been found to have antitubercular (Suresh Kumar, 2010), anti-HIV (Lazrek, 2001), anti-allergenic (Buckle, 1984), cytostatic (De las Heras, 1979), virostatic (Etrawy, 2010), anti-cancer (Holla, 2003), anti-convulsant (Chen, 2007), analgesic (Almajan, 2009) and anti-inflammatory (Erhan, 2002) activities. Triazoles are also being studied for the treatment of obesity (Poulsen, 2008) and osteoarthritis (Joshua, 2003). There are number of drugs, which are containing triazole nucleus, such as Fluconazole (Xu, 2009), Isavuconazole (Pasqualotto, 2008), Itraconazole (Alexander, 2010), Voriconazole (Smith, 2006), Pramiconazole (Geria, 2008), and Posaconazole (Schiller, 2007), that have been used for the treatment of fungal infection diseases. Owing to the immense importance and varied bioactivities exhibited by benzothiazepine and triazole derivatives and in continuation of our ongoing research on the synthesis of new heterocyclic compounds (Nagaraj, 2015, 2017), it was thought of interest to accommodate benzothiazepine and triazole moieties in a single molecular frame and to obtain a new heterocyclic compounds with potential biological activity. In this article, we wish to report the synthesis of a new class of 4-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-aryl-2,3-dihydro-1,5-benzothiazepine **6(a-j)** and evaluation of their *in vitro* antibacterial activity.

Corresponding author:* **Nagaraj, A.,
Department of Chemistry, Telangana University, Nizamabad, Telangana-503322 India

MATARIALS AND METHODS

All reagents are commercial grade and were used as supplied. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F_{254} plates from Merck, and compounds visualized by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded using KBr disk on a Perkin–Elmer FTIR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported in δ ppm units with respect to TMS as internal standard and coupling constants (*J*) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer.

Synthesis of phenylazide (3): To a cold solution of aniline 1 (1 mmol) in dil. hydrochloric acid (15 mL), sodium nitrite (1.1 mol) was added in small portions at 0-5 ^{o}C and stirred for one hour to afford the diazonium chloride **2,** then a solution of sodium azide (1.2 mol in 10 mL water) was added in drop wise manner and stirring was continued for 30 min and the resulting solid was filtered and recrystallized from ethanol to gave pure compound **3**. Yield 69%; IR (KBr) ν_{max}: 3110, 2167, 1610, 1277 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.10-7.20 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 117.3, 122.9, 130.1, 140.2; MS: *m/z* 119 (M^+).

Synthesis of 1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-ethanone (4): Compound **3** (1 mmol), acetyl acetone (4 mmol), anhydrous potassium carbonate (6 mmol), and DMF (30 mL) were added to a round bottom flask equipped with a stirrer. The reaction mixture was agitated at 70 ^{0}C for 6–12 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was removed under vacuum. The residual mass was quenched in the ice–water mixture and neutralized with 5% HCl solution. The product was extracted with dichloromethane dried over anhydrous sodium sulfate. Evaporation of the solvent yielded the crude product, which was purified by flash chromatography on silica gel eluted with petroleum ether/ethyl acetate (8:1-6:1). IR (KBr) ν_{max}: 3057, 2978, 1714, 1619, 1548, 1467 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 7.40-7.50 (m, 5H, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.9, 29.6, 114.7, 128.8, 129.1, 134.3, 139.0, 139.9, 193.1; MS: *m/z* 199 (M^+).

General procedure for the synthesis of (*E*)-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-3-aryl-2-propen-1-one (5a-j): A solution of **4** (1 mmol) and arylaldehyde (1 mmol) in 20 mL ethanol was slowly treated with 20 mL of 60% aqueous KOH solution at 5-10°C. The reaction mixture was stirred at room temperature until TLC indicated complete conversion (4h). It was then diluted with 50 mL water and extracted with 3x20 mL diethyl ether. The aqueous solution was acidified with dilute HCl. The solid obtained was filtered, washed thoroughly with water and dried. Crystallization of the crude residue from toluene: MeOH (3:2).

(*E*)-1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-3-phenyl-2-propen-1-one (5a): Yield 59%, mp 183-185 ^{o}C; IR (KBr) ν_{max}: 3012, 2961, 1702, 1621, 1549, 1424 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.61 (s, 3H, CH_3), 7.05-7.15 (m, 7H, Ar-H), 7.40-7.45 (m, 4H, CH=C, ArH), 7.83 (d, *J* = 12.4 Hz, 1H, CH=C); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 17.1, 102.9, 105.9, 116.9, 127.7 128.7, 129.4, 133.2, 133.8, 135.1, 138.1, 144.1, 147.4, 182.7; MS: *m/z* 287 (M^+).

General procedure for the synthesis of 4-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-aryl-2,3-dihydro-1,5-benzothiazepine 6(a-j): Ethanolic solution (50 mL) of compound 5(a-j) (1 mmol) was refluxed with 2-amino-thiophenol (1 mmol) and few drops of glacial acetic acid for 4 h. At the end of the reaction, the ethanolic solution was concentrated to half of its volume under reduced pressure. The solid that separated from the concentrate was filtered and recrystallized from benzene: petrol ether (8:2 v/v) to get compounds 6(a-j).

4-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-phenyl-2,3-dihydro-1,5-benzothiazepine (6a): Yield 44%; IR (KBr) ν_{max}: 3067, 2977, 1623, 1548, 1460, 674 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.69 (s, 3H, CH_3), 3.02 (t, *J* = 11.4 Hz, 1H), 3.17 (dd, *J* = 4.3, 12.9 Hz, 1H), 4.91 (dd, *J* = 4.3, 12.1 Hz, 1H), 7.20-7.55 (m, 14H, Ar-H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.7, 39.8, 58.6, 122.9, 124.5, 126.4, 127.1, 127.9, 128.0, 128.7, 129.0, 129.8, 135.9, 136.8, 143.6, 144.6, 149.9, 153.2; MS: *m/z* 396 (M^+).

2-(4-Chlorophenyl)-4-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2,3-dihydro-1,5-benzothiazepine (6b): Yield 39%; IR (KBr) ν_{max}: 3071, 2978, 1621, 1542, 1461, 673, 689 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.52 (s, 3H, CH_3), 3.03 (t, *J* = 11.3 Hz, 1H), 3.18 (dd, *J* = 4.1, 12.3 Hz, 1H), 4.90 (dd, *J* = 4.3, 12.1 Hz, 1H), 7.20-7.55 (m, 13H, Ar-H); MS: *m/z* 430 (M^+).

2-(4-Methylphenyl)-4-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2,3-dihydro-1,5-benzothiazepine (6c): Yield 41%; IR (KBr) ν_{max}: 3074, 2979, 1619, 1539, 1463, 671 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.04 (t, *J* = 11.5 Hz, 1H), 3.10 (dd, *J* = 4.2, 12.6 Hz, 1H), 4.89 (dd, *J* = 4.2, 12.4 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.20-7.55 (m, 11H, Ar-H); MS: *m/z* 410 (M^+).

4-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-(4-nitrophenyl)-2,3-dihydro-1,5-benzothiazepine (6d): Yield 44%; IR (KBr) ν_{max}: 3072, 2980, 1622, 1536, 1467, 1372, 673 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.53 (s, 3H, CH_3), 3.04 (t, *J* = 11.6 Hz, 1H), 3.11 (dd, *J* = 4.3, 12.4 Hz, 1H), 4.87 (dd, *J* = 4.4, 12.6 Hz, 1H), 7.20-7.55 (m, 11H, Ar-H), 7.82 (d, *J* = 8.7 Hz, 2H, Ar-H); MS: *m/z* 441 (M^+).

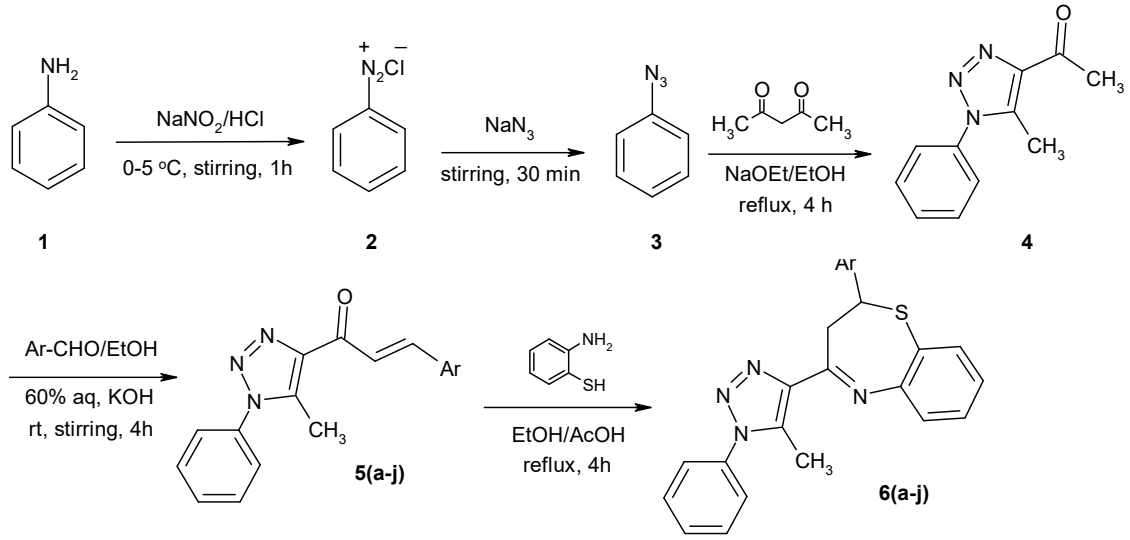
2-(4-Methoxyphenyl)-4-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2,3-dihydro-1,5-benzothiazepine (6e): Yield 51%; IR (KBr) ν_{max}: 3074, 2979, 1624, 1533, 1466, 1071, 677 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.54 (s, 3H, CH_3), 3.05 (t, *J* = 11.4 Hz, 1H), 3.17 (dd, *J* = 4.7, 12.3 Hz, 1H), 3.74 (s, 3H, OCH_3), 4.88 (dd, *J* = 4.5, 12.8 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.20-7.55 (m, 11H, Ar-H); MS: *m/z* 426 (M^+).

2-[4-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2,3-dihydro-1,5-benzothiazepin-2-yl]phenol (6f): Yield 48%; IR (KBr) ν_{max}: 3429, 3076, 2977, 1622, 1534, 1463, 677 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.57 (s, 3H, CH_3), 3.06 (t, *J* = 11.3 Hz, 1H), 3.19 (dd, *J* = 4.5, 12.1 Hz, 1H), 4.89 (dd, *J* = 4.4, 12.6 Hz, 1H), 5.18 (bs, 1H, OH), 6.77-6.78 (m, 2H, Ar-H), 7.20-7.55 (m, 11H, Ar-H); MS: *m/z* 412 (M^+).

***N*,*N*-Dimethyl-*N*-4-[4-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2,3-dihydro-1,5-benzothiazepin-2-yl]phenylamine(6g):** Yield 41%; IR (KBr) ν_{max}: 3072, 2979, 1621, 1532, 1467, 679 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.53 (s, 3H, CH_3), 2.91 (s, 6H, CH_3), 3.04 (t, *J* = 11.3 Hz, 1H), 3.14 (dd, *J* = 4.2, 12.3 Hz, 1H), 4.88 (dd, *J* = 4.5, 12.4 Hz, 1H), 6.44 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.20-7.55 (m, 11H, Ar-H); MS: *m/z* 439 (M^+).

4-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-(2-pyridyl)-2,3-dihydro-1,5-benzothiazepine (6h): Yield 43%; IR (KBr) ν_{max}: 3089, 2991, 1627, 1536, 1474, 681 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.57 (s, 3H, CH_3), 3.06 (t, *J* = 11.1 Hz, 1H), 3.17 (dd, *J* = 4.3, 12.7 Hz, 1H), 4.89 (dd, *J* = 4.4, 12.8 Hz, 1H), 7.20-7.55 (m, 12H, Ar-H), 8.43 (d, J = 8.7 Hz, 1H, Ar-H); MS: *m/z* 397 (M^+).

2-(2-Furyl)-4-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2,3-dihydro-1,5-benzothiazepine (6i): Yield 32%; IR (KBr) ν_{max}: 3091, 2987, 1629, 1541, 1481, 684 cm^{-1}. ^{1}H-NMR (300 MHz,



5/6: Ar = a) phenyl; b) 4-chlorophenyl; c) 4-methylphenyl; d) 4-nitrophenyl; e) 4-methoxyphenyl; f) 2-hydroxyphenyl; g) 4-dimethylaminophenyl; h) 2-pyridyl; i) 2-furyl; j) 2-thienyl

Scheme 1. Schematic route for the synthesis of compounds 6(a-j)

DMSO-d_6): δ 2.58 (s, 3H, CH_3), 3.08 (t, J = 11.4 Hz, 1H), 3.19 (dd, J = 4.0, 12.3 Hz, 1H), 4.91 (dd, J = 4.6, 12.2 Hz, 1H), 5.91 (d, J = 6.4 Hz, 1H, Ar-H), 6.21 (dd, J = 6.4, 9.2 Hz, 1H, Ar-H), 7.20-7.55 (m, 10H, Ar-H); MS: *m/z* 386 (M^+).

4-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-(2-thienyl)-2,3-dihydro-1,5-benzothiazepine (6j): Yield 38%; IR (KBr) ν_{max}: 3093, 2988, 1626, 1547, 1478, 681 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.55 (s, 3H, CH_3), 3.04 (t, J = 11.3 Hz, 1H), 3.21 (dd, J = 4.2, 12.7 Hz, 1H), 4.91 (dd, J = 4.5, 12.7 Hz, 1H), 5.93 (d, J = 6.6 Hz, 1H, Ar-H), 6.40-6.50 (m, 2H, Ar-H) 7.20-7.55 (m, 9H, Ar-H); MS: *m/z* 402 (M^+).

RESULTS AND DISCUSSION

The diazotization of aniline 1 by nitrous acid at 0-5 ^{0}C in the presence of HCl for 1 h, led to the formation of phenyldiazonium chloride 2, which on reaction with sodium azide at stirring for 30 min. produced phenylazide 3. It was reported that the azide compound can be cyclized using ethyl acetoacetate to furnish 1,2,3-triazole derivative. In a similar fashion the azide 3 was cyclized with acetylacetone in the presence of sodium ethoxide in ethanol at reflux for 4 h, to afford 1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-ethanone 4. The structure of compound 4 was confirmed by its EI mass, IR, ^{1}H NMR and ^{13}C NMR spectral data. In the proton NMR spectra showed a signal corresponding to the aromatic protons at δ 7.40-7.50 ppm as multiplet for five protons. The protons of methyl group at triazole ring appeared at δ 2.87 as a singlet for three protons, the acetyl group proton appeared at δ 2.32 as singlet. Its ^{13}C NMR specta showed the signals corresponding to the carbons of triazole ring at δ 129.1 and 134.3, the signal of carbonyl carbon in acetyl group appeared at δ 192.1 ppm. The IR spectrum showed absorption bands at 1714 and 1548 cm^{-1} due the C=O and C=N. The condensation of 4 with corresponding aryl/heteryl aldehyde at 5-10 ^{0}C in the presence of 60% aq. KOH in ethanol for 4 h, led to the formation of (*E*)-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-3-aryl-2-propen-1-one (5a-j), which on cyclio-condensation with 2-amino-thiophenol in the presence of acetic acid in ethanol at reflux temperature for 4 h, to afford 4-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-aryl-2,3-dihydro-1,5-benzothiazepine 6(a-j) (Scheme 1). The structure of compounds was confirmed by its EI mass, IR and NMR spectral data.

The IR spectrum of 5a showed a characteristic absorption band at 1702 cm^{-1} due to carbonyl (C=O) stretching. It's proton NMR spectrum reveals the presence of one equivalent protons of a methyl group at δ 2.61 and exhibit presence of olefinic protons as a doublet at δ 7.32 and 7.83 regions with a mutual coupling constant value 12.4 Hz. These observed coupling constant values indicate the presence of *E*,*E*-configuration, the remaining aromatic proton appears at their respective position. The IR spectra of compound 6a reveals absorption band in the region 1460 cm^{-1} which may be assigned to C=N beside the absence of carbonyl absorption band of 5a at 1702 and 678 cm^{-1} due to C-S-C stretching. Its ^{1}H NMR spectra, the CH_3 proton absorbed as a singlet at δ 2.69 and the triplet at δ 3.02 with coupling constant 11.4 Hz due to C_2-H of thiazepine ring and δ 3.17 showed doublet of doublet with coupling constants 4.3, 12.9 Hz due to C_3-H thiazepine ring and doublet of doublet at δ 4.91 with coupling constants 4.3, 12.1 Hz for 1H proton and rest of the aromatic proton appear at their respective position.

Antibacterial Activity

The *in vitro* antibacterial activities of newly synthesized compounds 6(a-j) were assessed against Gram-positive bacteria *viz*. *Bacillus subtilis*, *Bacillus sphaericus* and *Staphylococcus aureus*, and Gram-negative bacteria *viz*. *Pseudomonas aeruginosa*, *Klobsinella aerogenes* and *Chromobacterium violaceum* by broth dilution method recommended by National Committee for Clinical Laboratory Standards (Villanova, 1982). Bacteria were grown overnight in Luria Bertani (LB) broth at 37°C, harvested by centrifugation, and then washed twice with sterile distilled water. Stock solutions of the series of compounds were prepared in DMSO. Each stock solution was diluted with standard method broth (Difco) to prepare serial two-fold dilutions in the range of 100 to 0.8 μg/mL. Ten microliters of the broth containing about 10^5 colony-forming units (cfu)/mL of test bacteria wasere added to each well of a 96-well microtiter plate. Culture plates were incubated for 24 h at 37 °C, and the growth was monitored by visually and spectrophotometrically. Penicillin and Streptomycin were also screened under identical conditions for comparison. The minimal inhibitory concentration (MIC, μg/mL) of the compounds 6a-j are presented in Table 1.

Table 1. Antibacterial activity of compounds 6(a-j)

Compound	Minimum inhibitory concentration (MIC, μ/mL)					
	B. subtilis	*B. sphaericus*	*S. aureus*	*P. aeruginosa*	*K. aerogenes*	*C. violaceum*
6a	12.5	12.5	25	--	12.5	25
6b	6.25	6.25	6.25	25	12.5	6.25
6c	6.25	12.5	12.5	25	25	25
6d	6.25	6.25	12.5	25	12.5	12.5
6e	6.25	6.25	12.5	--	6.25	6.25
6f	6.25	6.25	6.25	25	6.25	12.5
6g	25	12.5	6.25	12.5	12.5	25
6h	25	25	6.25	12.5	25	25
6i	12.5	6.25	6.25	12.5	25	25
6j	6.25	12.5	25	--	12.5	25
Streptomycin	6.25	12.5	6.25	1.56	1.56	3.12
Penicillin	1.56	3.12	1.56	6.25	6.25	12.5

It has been observed that the compounds exhibited interesting biological activity however, with a degree of variation. In the series 6a-j, the compounds 6b, 6e were found to be the most active against Gram-positive and Gram-negative bacteria. The compound 6f is highly active against all the three Gram-positive bacteria and *K.aerogens*, the compounds 6d is active against *B. subtilis* and 6d and 6f were active against *B.sphaericus*. The remaining compounds showed moderate to good activity against all the organisms employed except *P.aeruginosa*.

Conclusion

A new series of 4-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-aryl-2,3-dihydro-1,5-benzothiazepine 6(a-j) have been synthesized and evaluated for their antibacterial activity against various bacterial strains. The screened compounds 6 which contain 4-chlorophenyl (6b), 4-methoxyphenyl (6e) and 2-hydroxyphenyl (6f) moieties on thiazepine ring exhibited potent antibacterial activity compared to standard drug at the tested concentrations. The other compounds also showed appreciable activity against the test bacteria and emerged as potential molecules for further development.

Acknowledgements

The authors are thankful to the Director, Indian Institute of Chemical Technology, Hyderabad, India, for providing NMR and mass spectral data.

REFERENCES

Alexander, A., Tom, P., Caremans, J.V., Guy Van den, M., Johan, A.M. and Patrick, A. 2010. "Growth of itraconazole nanofibers in supersaturated simulated intestinal fluid randy mellaerts" *Molecular Pharmaceutics*, Vol. 7, No. 3, pp. 905-913.

Almajan, G.L., Barbucenau, S.F., Almajan, E.R., Draghici, C. And Saramet, G. 2009. "Synthesis, characterization and antibacterial activity of some triazole Mannich bases carrying diphenylsulfone moieties" *European Journal of Medicinal Chemistry*, Vol. 44, No. 7, pp. 3083-3089.

Bohrisch, J., Faltz, H., Patzel, M. and Liebscher, J. 1994. "Chiral 1,4-diazepinones and 1,4-thiazepinones by dia-stereoselective ring chain tansformation of α,β unsaturated lactones or lactams" *Tetrahedron*, Vol. 50, No. 36, pp. 10701-10708.

Bruckle, D.R., Rockell, C.J., Smith, H. and Spicer, B.A. 1984. "Studies on 1,2,3-triazoles: synthesis and antiallergic properties of 9-oxo-1*H*,9*H*-benzothiopyrano[2,3-*d*]1,2,3-triazoles and their *S*-oxides" *Journal of Medicinal Chemistry,* Vol. 27, No. 2, pp. 223-227.

Chen, J., Sun, X.Y., Chai, K.Y., Lee, J.S., Song, M.S. And Quan, Z.S. 2007. "Synthesis and anticonvulsant evaluation of 4-(4-alkoxyphenyl)-3-ethyl-1*H*-1,2,4-triazoles as open-chain analogues of 7-alkoxyl-4,5-dihydro[1,2,4]triazolo [4,3-*a*]quinolines" *Bioorganic and Medicinal Chemistry*, Vol. 15, No. 21, pp. 6775-6781.

Chiesi, M., Schwaller, R. and Eichenberger. K, 1988. "Structural dependency of the inhibitory action of benzodi-azepines and related compounds on the mitochondrial Na^{+}-Ca^{2+} exchanger" *Biochemical Pharmacology*, Vol. 37, No. 22, pp. 4399-4403.

De las Heras, F.G., Alonso, R. and Alonso, G. 1979. "Alkylating nucleosides: synthesis and cytostatic activity of *N*-glycosyl(halomethyl)-1,2,3-triazoles: A new type of alkylating agent" *Journal of Medicinal Chemistry*, Vol. 22, No. 5, pp. 496-501.

El-Etrawy, A.S. and Abdel-Rahman, A.A.H. 2010. "Synthesis and antiviral evaluation of 1,3-dimethyl-6-(1*H*-1,2,3-triazol -1-yl)pyrimidine-2,4(1*H*,3*H*)-dione derivatives", *Chemistry of Heterocyclic Compounds*, Vol. 46, No. 9, pp. 1105-1108.

Erhan, P., Gülay, S., Pelin, K., Tuğba, D. and Gülçin, A. 2002, "Synthesis and anti-inflammatory activity of 1-acylthio semicarbazides, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazole-3-thiones" *Il Farmaco*, Vol. 57, No. 2, pp. 101-107.

Feng, S., Xiao, N.Z., Xu, D.C., Shu, Z. and Shu, J.T. 2012. "Design and diversity-oriented synthesis of novel 1,4-thiazepan-3-ones fused with bioactive heterocyclic skeletons and evaluation of their antioxidant and cytotoxic activities" *Bioorganic and Medicinal Chemistry Letters*, Vol. 22, No. 1, pp. 743-746.

Geria, A.N. and Scheinfeld, N.S. 2007. "Pramiconazole, a triazole compound for the treatment of fungal infections" *Drugs*, Vol. 11, No, 9, pp. 661-670.

Glaser, R. and Sklarz, B. 1989. "Stereochemistry and conformation in solution of diltiazem hydrochloride, a 1,5-benzothiazepine coronary vasodilator" *Journal of The Chemical Society-perkin Transactions 2*, No. 8, pp. 29890001031.

Holla, B.S., Veeranna, B., Shivananda, M.K. and Poojary, B. 2003. "Synthesis characterization and anticancer activity studies on some Mannich bases derived from 1,2,4-triazoles" *European Journal of Medicinal Chemistry*, Vol. 38, No. 7-8, pp. 759-767.

Inoue, H., Kugita, H., Ikezaki, M., Konda, M., Takeo, S. 1971. "Synthesis of 1,5-benzothiazepine derivatives. III, *Chemical Pharmaceutical Bulletin*. Vol. 19, No. 3, 595-602.

Inoue, H., Konda, M., Hashiyama, T., Otsuka, H., Takahashi, K., Gaino, M., Date, T., Aoe, K., Taked, M., Murata, S., Narita, H. and Nagao, T. 1991. "Synthesis of halogen-substituted 1,5-benzothiazepine derivatives and their vasodilating and hypotensive activities" *Journal of Medicinal Chemistry*, Vol. 34, No. 2, pp. 675-687.

Joshua, S.T., John, C.V.R., Michael, G.N., Michael, P.C., Biswanath, De., Lily, C.H. and Michael, J.J. 2003. "The development of new triazole based inhibitors of tumor necrosis factor-α (TNF- α) production" *Bioorganic and Medicinal Chemistry Letters*, Vol. 13, No. 8, pp. 1609-1618.

Lazrek, H.B., Taourirte, M., Oulih, T., Barascut, J.L., Imbach, J.L., Pannecouque, C., Witrouw, M. and De Clercq. 2001. "Synthesis and anti-HIV activity of new modified 1,2,3-triazole acyclonucleosides" *Nucleosides Nucleotides Nucleic Acids*, Vol. 20, No. 12, pp. 1949-1960.

Nagaraj, A., Aparna, M., Ramesh Naik, P., Raghuveer, S. and Nageswara Rao, G. 2017. "Design, Synthesis and antibacterial activity of novel pyrazolyl dihydropyrimidinones" *International Journal of Current Research*, Vol. 9, No. 12, pp. 62361-62365.

Nagaraj, A., Aparna, M., Ramesh Naik, P., Nageswara Rao, G. and Raghuveer, S. 2017. "Synthesis of new [1,2,4] triazolo[4,3-*d*][1,2,3,4]thiatriazoles as potential antibacterial agents" *Journal of Chemistry and Chemical Sciences*, Vol. 7, No. 9, pp. 676-686.

Nagaraj, A., Aparna, M., Ramesh Naik, P., Raghuveer, S. and Nageswara Rao, G. 2017, "Synthesis and antibacterial evaluation of new thiazolo[4,5-c]isoxazole bearing morpholine" *Journal of Chemistry and Chemical Sciences*, Vol.7, No. 12, pp. 1087-1096.

Nagaraj, A., Sunitha, M., Sanjeeva Rao, L., Vani Devi, M. and Sanjeeva Reddy, Ch. 2015. "Synthesis and biological evaluation of 3-benzyl/piperazinomethyl-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione" *Organic Communications*, Vol. 8, No. 3., pp. 70-77.

Oster, G., Huse, D.M., Adams, S.F., Imbimbo, J. and Russell, M.W. 1990. "Benzodiazepine tranquilizers and the risk of accidental injury" *American Journal of Public Health*, Vol. 80, No. 12, pp. 1467-1470.

Pasqualotto, A.C. and Denning, D.W. 2010. **"**New and emerging treatments for fungal infections" *Journal of Antimicrobial Chemotherapy, Vol.* 61, No. 1, pp. i19-i30.

Poulsen, S.A., Wilkinson, B.L. and Innocenti, A. 2008. "Inhibition of human mitochondrial carbonic anhydrases VA and VB with para-(4-phenyltriazole-1-yl)-benzene sulphonamide derivatives" *Bioorganic and Medicinal Chemistry Letters*, Vol. 18, No. 16, pp. 4624-4627.

Reddy, J.R., Ashok, D. and Sharma, P.N. 1993. "Synthesis of 4,6-bis(2'-substituted-2',3'-dihydro-1,5-benzothiazepin-4'-yl)resorcinols as potential antifeedents" *Indian Journal of Chemistry*, Vol. 32B, No. 9, 404-406.

Renuka, N., Pavithra, G. and Ajay Kumar, K. 2014. "Synthesis and their antioxidant activity studies of 1,4-benzothiazepine analogues" *Der Pharma Chemica*, Vol. 6, No. 1, pp. 482-485.

Sachio, O., Kihachiro, I., Kiyoshi, M., Kazuo, K. and Mikio, H. 1983. "Synthesis of a new potent anti-ulcer and gastric secretory inhibiting agent, (-)-cis-2,3-dihidro-3-(4-methyl-piperazinylmethyl)-2-phenyl-1,5-benzothiazepin-4(5*H*)-one hydrochloride (BTM-1086), and related compounds" *Chemical Pharmaceutical Bulletin*. Vol. 31, No. 5, 1780-1783.

Schiller, D.S. and Fung, H.B. 2007. "Posaconazole: an extended-spectrum triazole antifungal agent" *Clinical Therapeutics*, Vol. 29, No. 9, pp. 1862-1886.

Smith, J., Safdar, N., Knasinski, V., Simmons, W., Bhavnani, S.M., Ambrose, P.G., Andes, D. 2006. "Voriconazole therapeutic drug monitoring" *Antimicrobial Agents Chemotherapy*, Vol. 50, No. 4, pp. 1570-1572.

Suzuki, T., Ohashi, M., Takaiti, O. and Harigaya, S. 1994. "Calmodulin antagonistic action of new 1,5-benzothiazepines derived from diltiazem" *Arzneimittel-Forschung*, Vol. 44, No. 1, pp. 3-6.

Suresh Kumar, G.V., Rajendra Prasad, Y., Mallikarjuna, B.P., Chandrashekar, S.M. and Kishtaiah, C. 2010. "Synthesis of some novel 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4-oxadiazoles as potential antimicrobial and antitubercular agents" *European Journal of Medicinal Chemistry*, Vol. 45, No. 5, pp. 2063-2074.

Vega, S., Diaz, J.A., Darias, V. Sanchez Mateo, C.C. and Albertos, L.M. 1998. "Antidepres- sant activity of new hetero[2,1]benzothiazepine derivatives" *Pharmazie*, Vol. 53, No. 2, 130-134.

National Committee for Clinical Laboratory Standards (NCCLS). Standard methods for dilution antimicrobial susceptibility tests for bacteria, which grows aerobically. 1982. *Nat. Comm. Lab. Stands*. Villanova, pp. 242,

Vyawahare, D., Ghodke, M. and Nikalje, A. 2010. "Green synthesis and pharmacological screening of novel 1,5-Benzothiazepines as CNS agents" *International Journal of Pharmacy and Pharmaceutical Sciences*,Vol. 2. No. 2, pp. 27-29.

Wang, L., Zhang, P. Zhang, X., Zhang, Y., Li, Y. and Wang. Y. 2009. "Synthesis and biological evaluation of a novel series of 1,5-benzothiaepine derivatives as potential antimicrobial agents" *European Journal of Medicinal Chemistry*, Vol. 44, No. 7, pp. 2815-2821.

Xu, Y.W., Yan, Y., Lan, L., Rong, M.D., Bao, D.T. Ren, J.G. Ping, H.J. and Yuan, Y. 2009. "Proteomic analysis reveals a synergistic mechanism of fluconazole and berberine against fluconazole-resistant Candida albicans: Endogenous ROS Augmentation" *Journal of Proteomic Research, Vol.* 8, No. 11, pp. 5296-5304.

****